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Multi nutrient functional biscuits "Tumiz" improve nutritional status and growth of children; A clinical trial in malnourished rats

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ABSTRACT

Background: The main cause of malnutrition in Indonesia is insufficient nutrient intake, necessitating efforts to supplement nutrients through supplementary feeding. Conversely, Indonesia possesses a variety of local food ingredients that remain underutilized, thus requiring processing to enrich the nutrient content of snacks for combating malnutrition. Previously, we have developed flour-fortified biscuits from local food ingredients that contain complete nutrients (Tumiz). Objectives. This study aims to assess the impact of Tumiz functional biscuits on the nutritional status and growth malnourished Wistar rats.

Methods: Employing a randomized control group pretest-posttest design, male Wistar rats divided into four groups, each comprising 6 samples. These groups included K1: normal rats fed standard food, K-2: malnourished rats given biscuits from the Ministry of Health program, K-3: malnourished rats fed normal food, and K-4: malnourished rats given Tumiz biscuits. The intervention spanned eight weeks, during which body weight, body length, albumin, and IGF-1 levels were measured before and after the intervention.

Results: Significant increases in body weight were observed between pretest-posttest in all groups: K1 (p=0.003), K2 (p=0.006), K3 (p=0.003), and K4 (p=0.003). The greatest increase in body weight over two months was found in group K4. The albumin levels increased in the rats, there was no statistically significant difference in albumin levels before and after the intervention acrossall groups: K1 (p=0.336), K2 (p=0.297), K3 (p=0.191), and K4 (p=0.466). All intervention groups experienced a significant increase in body length (p<0.05), including groups K1 (p<0.001), K2 (p=0.003), K3 (p<0.001), and K4 (p<0.001). The increase in body length of group K4 did not differ from group K1. IGF-1 levels of Wistar rats significantly increased in group K4 (p=0.006) and group K2 (p=0.026), while groups K1 and K3 experienced a decrease in IGF-1 levels.

Conclusion: Tumiz biscuits can increase body weight, body length, and IGF-1 levels but have not been able to increase albumin levels in malnourished Wistar rats.

KEYWORDS

Animal models, biochemical markers, food supplementation, experimental research.

INTRODUCTION

Malnutrition, especially in children under five in the global including Indonesia, remains a significant public health problem requiring serious attention. The Nutrition Status Survey of Indonesia (SSGI) 2022 reported a prevalence of underweight of 17.7%, stunting of 29.9%, and wasting of 10.2%[1]. The primary cause of malnutrition is inadequate nutrient intake. Malnutrition during toddlerhood can lead to linear growth deficit, which has short and long term consequences for physical abilities and productivity[2]. Children experiencing growth deficit since in utero and continuing into the postnatal period are at risk of developing various degerative diseases[3]. Malnourished children under five (U5) commonly exhibit increased metabolism, leading to elevated oxidative stress[4].

Intervention strategies to address nutritional deficiencies in U5 children through balanced nutrition and supplementary

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foods may help prevent malnutrition and reduce oxidative stress[5]. Numerous prior studies demonstrated the benefits of utilizing local food sources[6], such as sago worms[7], soybeans, green beans[8,9], and vegetable like carrots[10] in tackling malnutrition. The advancements in food processing technology have facilitated the creation of nutritionally complete flour products, such as multi-nutrient flour (Tumiz)[11].

Tumiz is a functional food flour made from local food ingredients, namely soy bean flour, mung beans, carrots and sago worms so that it contains complete nutrients (multi nutrition). We have developed biscuits through Tumiz fortification so that it has more complete nutrients. Each piece of Tumiz functional biscuit contains 67 kcal energy, 2 g protein, 3.2 g fat, 2.2 mg vitamin A, 0.8 mg iron, 58 mg calcium, 3 mg zinc, 80%DPPH antioxidant[11,12]. Drawing upon the the positive outcomes of previous studies[14], we hypothesized that this biscuit could serve as a valuable nutritional intervention to improve the nutritional status of malnourished children.

Prior to implementation as intervention program to human, preclinical testing involving animal trials, specifically Wistar rat, is conducted. The outcome of this preclinical trial is expected to elucidate the effects of Tumiz biscuits on the growth dan nutritional status of experimental animals. The hypothesis posits that intervention with Tumiz biscuits can enhance growth and nutritional status in children under five. Looking ahead, multi-nutritional snacks hold promise as an alternative for enhancing nutritional status and combating nutritional challenges, especially among children under five.

METHOD

Research Design

This study was conducted with preclinical trials using a randomized controlled group pretest-posttest design, comprising four treatment groups. The intervention lasted for 8 weeks.

Sample

The experimental animals used as samples were Wistar white rats meeting the following criteria: Male sex, aged 5-8 weeks, weighing 100-160 grams, and exhibiting physical health characterized by smooth and clean fur, clear eyes and ears, and good appetite. The rats were procured from the Pharmacology Laboratory of the Faculty of Medicine, Hasanuddin University.

The sample size was calculated based on Freder's formula: (t-1)(n-1) ≥ 15, where (t=number of groups, n=size of each group, 15=general degrees of freedom). Therefore, the sample size was determined to be 6 rats in each group. Accounting for a 10% estimated mortality rate, the sample size for each group was set 7 rats, resulting in a total sample size of 28 rats.

The sample was divided into four groups. Selection of malnourished rats was conducted through simple random sampling, utilizing a lottery system. Group-1 (K1), consisted of normal rats fed standard food; group-2 (K2) comprised malnourished rats fed biscuits from the Ministry of Health program; group-3 (K3) involved malnourished rats fed standard food; and group-4 (K4) consisted of malnourished rats fed Tumiz biscuits.

This study was conducted in accordance with the ethical guidelines for animal research, as outlined in the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines and the International Guiding Principles for Biomedical Research Involving Animals. The research protocol was approved by the Health Research Ethics Commission (KEPK) of the Faculty of Medicine, Hasanuddin University (266/UN4.6.4.5.31/PP36/2023). All procedures involving animals adhered to the principles of 3Rs (Replacement, Reduction, Refinement) to minimize suffering and enhance animal welfare. The handling of rats was performed by trained personnel following standard operating procedures[15].

Research Treatment

Pre-treatment

Before initiating treatment, all Wistar rat samples underwent weighing and were acclimatized for one week. During the adaptation period, the rats were housed in cages measuring 40 x 20 x 10 cm^3, with a maximum of four rats per cage. The cage temperature was maintained at room temperature. Throughout the adaptation period, the rats were provided with 20 grams of pellets daily and drinking water was available ad libitum.

Pretreatment

Pretreatment was conducted to induce malnutrition conditions in the rats, characterized by a minimum weight loss of 5-10% of their normal body weight. Malnutrition conditions were induced by providing food with low protein content, specifically gogek made from grated cassava. Gogek, similar in size to cassava but smaller, was provided ad libitum at a dosage of 20 grams per day for 14 days. On the 14th day, weight, body length, and blood collection were measured for all samples.

Implementation of the Intervention

The intervention spanned eight weeks, during which the respective food regimens were administered according to group assignments. Feeding was conducted twice daily via a sonde for groups K2 and K4. Groups K1 and K3 were given standard food (AD I Super brand) equivalent to 10% of their body weight. Group K2 received biscuits from the government program (Ministry of Health), while group K4 was provided with Tumiz functional biscuits twice daily at a dosage of 5 grams per administration. The biscuits were initially pulverized using a blender, diluted to a concentration of 1:10, and administered via sonde.

Tumiz functional biscuits are made through the addition of Tumiz flour. The complete composition of Tumiz biscuit ingredients is as follows: 35% multi nutrition flour (Tumiz), wheat flour, powdered sugar, margarine, liquid milk, honey and baking powder[11,12].

Data Collection

Blood serum was collected for albumin and Insulin-like Growth Factor 1 (IGF-1) levels the day before the intervention (pretest) and at the end of week 8 (posttest). Body weight and body length measurements were taken at the beginning of the intervention (pre-test), week 4 (mid-test), and the end of week 8 (post-test). Body length was measured using a Kruuse brand animeter with a scale of 0.1 cm. Body weight was measured using Electronic Weighing Scale PCB model A-007 with a scale of 0.01 kg. Examination of albumin and IGF-1 levels were conducted using the ELISA method at the Hasanuddin University Medical Research Center (HUM-RC) Laboratory.

Albumin levels

Plasma was collected using EDTA or heparin as an anticoagulant. After mixing for 10-20 minutes, samples were centrifuged for 20 minutes at a speed of 2000-3000 RPM to collect the supernatant. Reagent preparation involved several stages: standard reconstitution, wash buffer dilution, and analysis steps, including the addition of standards and samples, incubation, washing, addition of substrate and stop solution, and measurement of optical density (OD) at 450 nm.

Insulin-like Growth Factor 1 (IGF-1) Level

Plasma was collected using EDTA or heparin as an anticoagulant. After centrifugation, samples were either tested immediately or stored at -20°C or -80°C. Reagent preparation involved dilution of standard, detection reagents A and B, wash solution, and TMB substrate. Analysis steps included the addition of standards and samples, incubation, washing, addition of detection reagents, washing, addition of substrate, addition of stop solution, and measurement of OD at 450 nm.

Data processing and analysis

Data from the study were inputted and processed through the IBM SPSS Statistics for Windows, Version 16.0 (IBM Corp, Armonk, New York, United States). Descriptive analysis was applied, and data was presented in mean and standard deviation. Data analysis was performed using a paired two-sample t-test to assess the effect of the intervention on body weight, body length, albumin, IGF-1, and MDA levels between before and after the intervention in each group, and a one-way ANOVA test to analyze differences in changes in body weight, body length, albumin, IGF-1 and MDA levels between groups. Data analysis used a significant level of 5% (α=0.05).

RESULTS

Nutritional Status

During the malnutrition stage, there was a decrease in body weight in groups K2, K3, and K4 of 23.40 kg, 23.98 kg, and 23.54 kg, respectively. No physical changes were observed in

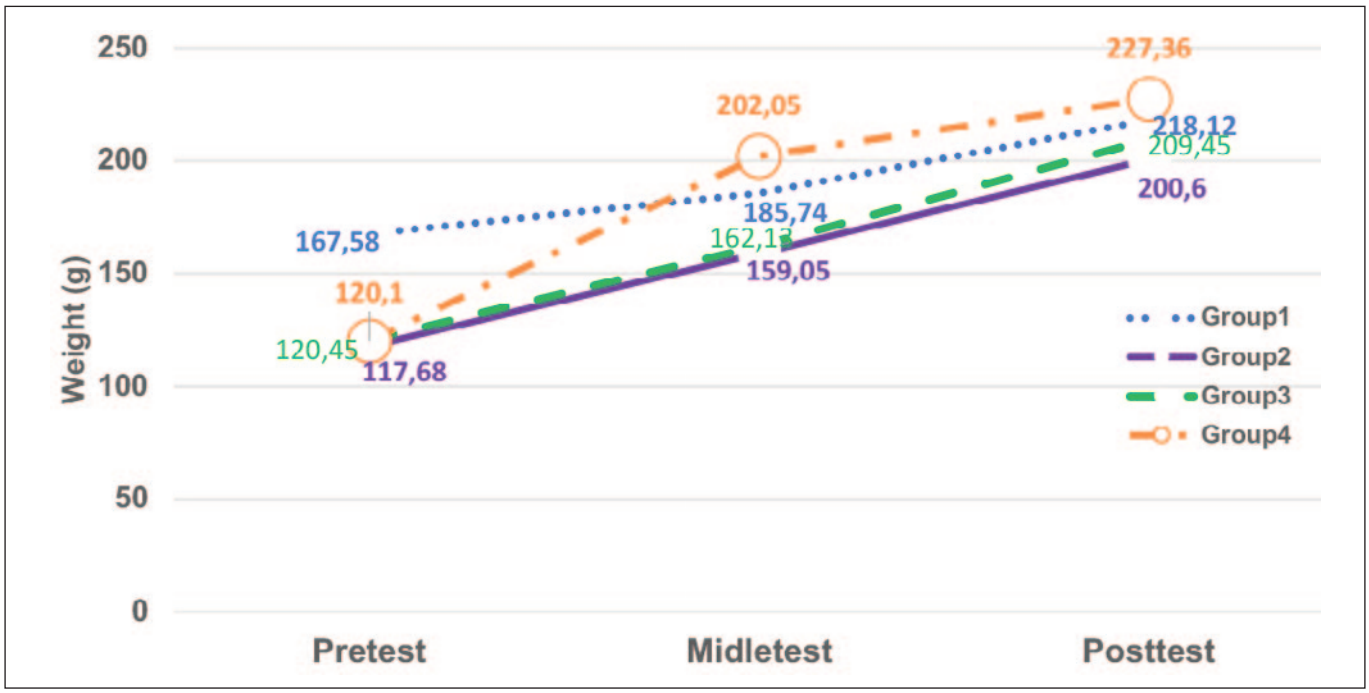

Figure 1. Mean body weight of Wistar rats during the intervention

the rats' fur during this stage, but they appeared less active and exhibited reduced movement. Conversely, rats in group K1 experienced an increase in body weight by 21.4 kg and appeared more agile and active.

The average body weight of K1 rats at the beginning of the intervention was higher than the other groups. However, in terms of weight gain, it can be seen that K4 had a higher weight gain at that stage, and was able to pass the weight of the normal rat group in the fourth week. The average body weight after 1 month of intervention in rats of group K1 = 185.74 g, K2 = 159.05 g, K3 = 162.13 g and K4 = 202.05 g.

After two months of intervention, each group had an average body weight as follows K1 = 218.12 g, K2 = 200.60 g, K3 = 209.45 g and K4 = 227.36 g, respectively. All groups increased during the intervention but Group K3 had a higher body weight.

The body weight of Wistar rats at pretest showed that group K1 weighed significantly higher than group K2 (p=0.002), K3 (p=0.002), and K4 (p<0.001). After one month of intervention, group K1 had an not insignificant weight gain (p=0.098). However, the other intervention groups experienced a significant increase in body weight: both groups K2 (p<0.001), K3 (p=0.005), and K4 (p<0.000). The highest weight gain after one month of intervention was found in group K4, significantly different from group K1 (p=0.009), but not significant from groups K2 and K3.

All intervention groups experienced an increase in body weight in the second month of intervention, but the amount of weight change in each group did not differ significantly between groups (p=0.827). Statistical analysis showed a significant increase in body weight of rats between pretest and posttest in K1 (p=0.003), K2 (p=0.006), K3 (p=0.003), and K4 (p=0.003). The greatest weight gain over two months was found in group K4, and the least in group K1.

Table 2 presents the albumin levels (mean ± standard deviation) of Wistar rats during the intervention. Group K2 exhibited higher final albumin levels (posttest), followed by group K4. Judging from the average increase in albumin levels during the first month of intervention (midtest), it appears that group K4

Table 1. Weight (g) of wistar rats between before and after intervention

Group	Before	Midle test	After	Δ	p-value[1]	p-value[2]
K1 (n=6)	167.58 ± 25.6	185.74 ± 31.8	218.1 ± 37.8	50.58 ± 21.9a	0.098	0.002**
K2 (n=6)	117.68 ± 14.9	159.05 ± 17.7	200.6 ± 30.3	82.70 ± 32.9ab	<0.001***	0.002**
K3 (n=6)	120.45 ± 11.4	162.13 ± 18.8	209.4 ± 35.1	89.00 ± 44.6ab	0.005**	0.002**
K4 (n=6)	120.10 ± 04.3	202.05 ± 23.3	227.4 ± 34.0	105.15 ± 43.2b	<0.001***	<0.001***
p-value[3]	0.000[ttt]	0.236	0.543	0.025[t]		

Description: Before, Midle test and After measurement results are mean ± standard deviation values; Δ = change in weight (g) between pre- and post-intervention; [1]Paired two-samples t-test with significant differences between pre- and midle-intervention at *p<0.05, **p<0.01, ***p<0.001; [2]Paired two-samples t-test with significant differences between pre- and post-intervention at *p<0.05, **p<0.01, ***p<0.001; [3]One-way ANOVA test with significant differences between group at [t]p<0.05, [tt]p<0.01, and [ttt]p<0.001.

Table 2. Albumin level (g/dL) of wistar rats between before and after intervention

Group	Before	After	Δ	p-value[1]
K1 (n=6)	31.528 ± 11.35	27.857 ± 4.69	-3.671 ± 8.44	0.336
K2 (n=6)	30.428 ± 8.12	41.925 ± 20.42	11.49 ± 26.22	0.297
K3 (n=6)	25.071 ± 6.31	20.694 ± 2.34	-4.376 ± 7.085	0.191
K4 (n=6)	25.768 ± 10.48	29.510 ± 6.23	3.741 ± 11.60	0.466
p-value[2]	0.649	[t]0.025[t]	0.226	

Description: Before, Midle test and After measurement results are mean ± standard deviation values; Δ = change in albumin between pre- and post-intervention; [1]Paired two-samples t-test with significant differences between pre- and midle-intervention; One-way ANOVA test with significant differences between group at [t]p<0.05.

experienced a greater increase in albumin levels. Conversely, groups K1 and K3 actually experienced a decrease in albumin levels during the first month of intervention. According to the results of statistical analysis, there was no difference in albumin levels between before and after the intervention in any of the groups: K1 (p=0.336), K2 (p=0.297), K3 (p=0.191), and K4 (p=0.466).

Growth

Graph 2 depicts a consistent increase in the body length of Wistar rats across all groups. Malnourished Wistar rats from group K4 exhibited a slightly higher body length gain compared to the other groups, although the difference was minimal.

Regarding the body length of Wistar rats at pretest, all groups had relatively similar body length (p=0.600). After one month of intervention, all groups experienced a significant increase in body length (p<0.05), including groups K1 (p=0.003), K2 (p=0.019), K3 (p<0.001) and K4 (p=0.015). The magnitude of change in body length of malnourished rats (K2, K3, K4) did not differ significantly from that of the normal rat group (K1).

Table 3. Body length (cm) status of wistar rats at the before and after intervention

Group	Before	Midletest	After	Δ	p-value[1]	p-value[2]
K1 (n=6)	17.9 ± 1.20	20.0 ± 0.70	21.85 ± 1.00	21.85 ± 1.00	0.001**	<0.001***
K2 (n=6)	18.0 ± 0.71	18.75 ± 0.90	21.75 ± 1.00	21.75 ± 1.00	0.016*	0.001**
K3 (n=6)	17.3 ± 0.26	20.13 ± 0.70	21.12 ± 1.00	21.12 ± 1.00	0.013*	<0.001***
K4 (n=6)	18.1 ± 0.20	21.5 ± 0.70	22.50 ± 0.60	22.50 ± 0.60	0.002**	<0.001***
p-value[3]	0.285	0.579	0.251	0.251		

Description: Before, Midle test and After measurement results are mean ± standard deviation values; Δ = change in body length (cm) between pre- and post-intervention. [1]Paired two-samples t-test with significant differences between pre- and midle-intervention at *p<0.05, **p<0.01, ***p<0.001. [2]Paired two-samples t-test with significant differences between pre- and post-intervention at *p<0.05, **p<0.01, ***p<0.001. [3]One-way ANOVA test with significant differences between group.

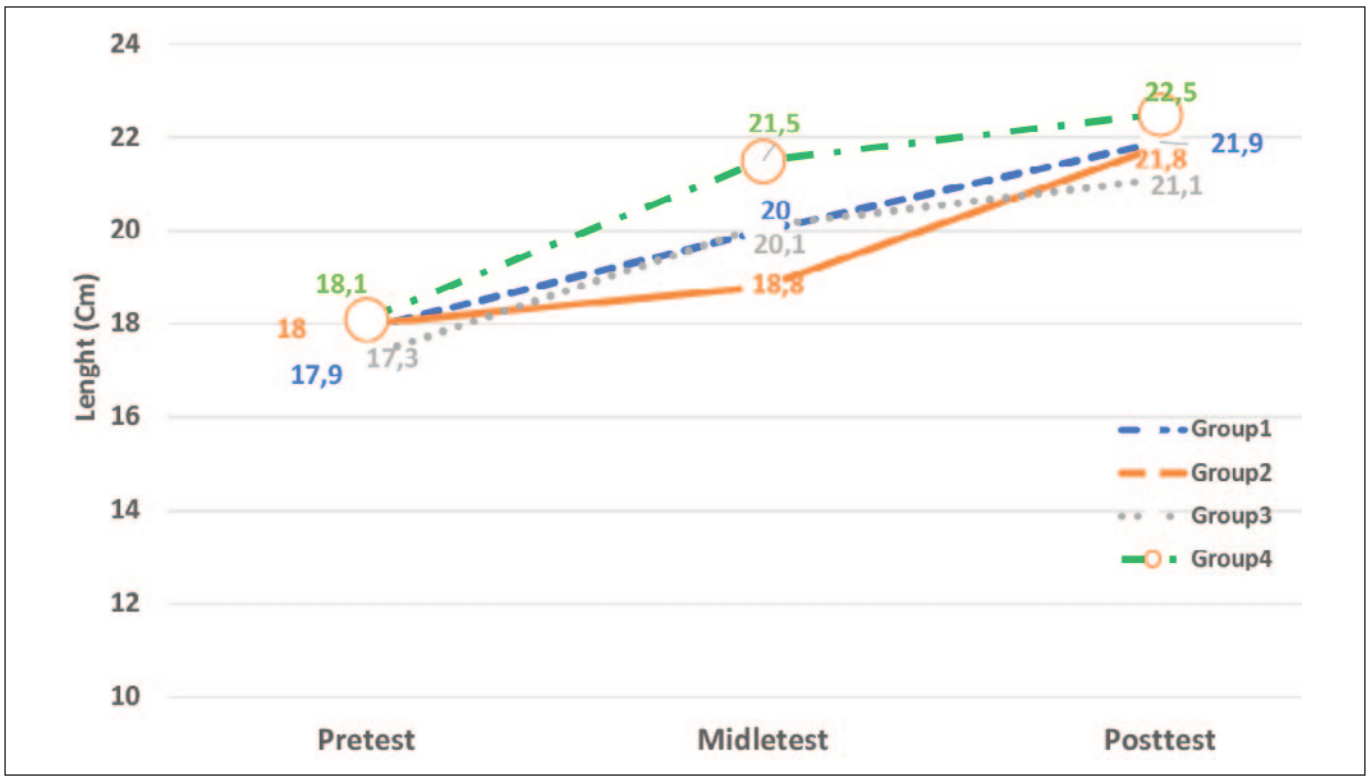

Figure 2. Mean body length (cm) of Wistar rats during intervention

After two months of intervention, all intervention groups experienced a significant increase in body length ($p<0.05$), including groups K1 ($p<0.001$), K2 ($p=0.001$), K3 ($p<0.001$), and K4 ($p<0.001$). The increase in body length of group K4, which received the Tumiz biscuits intervention, did not differ siginifcantly from that of the normal Wistar rat group (K1).

Table 4 presents the IGF-1 levels of Wistar rats during the intervention. Initial IGF-1 levels (pretest) indicated that group K1 rats had significantly higher IGF-1 levels than other groups ($p=0.002$). After completion of the intervention, it was observed that K4 had significantly higher final IGF-1 levels (post-test) than the other groups ($p=0.005$). IGF-1 levels of Wistar rats increased significantly in group K4 ($p=0.006$) and group K2 ($p=0.026$). Conversely, the K1 and K3 groups experienced a decrease in IGF-1 levels.

Table 4. IGF-1 level (µg/ml) of wistar rats between before and after intervention

Group	Before	After	Δ	p-value[1]
K1 (n=6)	4.597 ± 0.976	2.575 ± 1.701	-2.021 ± 1.384	0.016**
K2 (n=6)	1.857 ± 1.044	4.220 ± 1.176	2.360 ± 2.058	0.026**
K3 (n=6)	2.155 ± 1.708	2.034 ± 0.815	-0.121 ± 1.626	0.862
K4 (n=6)	2.198 ± 0.641	4.251 ± 0.726	2.052 ± 1.096	0.006*
p-value[2]	0.002[tt]	0.005[tt]	<0.000[ttt]	

Description: Before and After measurement results are mean ± standard deviation values; Δ = change IGF-1 between pre- and post-intervention; [1]Paired two-samples t-test with significant differences between pre- and post-intervention at *p<0.05, **p<0.01, ***p<0.001; [2]One-way ANOVA test with significant differences between group at [t]p<0.05, [tt]p<0.01, and [ttt]p<0.001.

DISCUSION

Nutritional Status

The average body weight of K1 rats at the beginning of the intervention was higher than the other groups. This discrepancy arose because Wistar rats in groups K2, K3, and K4 experienced a weight loss of about 23 grams during the malnutrition process. However, after the 8-week intervention, there was an increase in body weight in all groups. Notably, the increase in body weight of the K4 group, which received Tumiz biscuit intervention, was higher than the other groups. Feeding Tumiz biscuits demonstrated the capacity to increase the body weight of malnourished Wistar rats, effectively restoring their nutritional status. Furthermore, the body weight of K4 rats that received Tumiz biscuits intervention exceeded that of the normal rat group (K1), indicating the superior effects of Tumiz biscuits in increasing the body weight of malnourished Wistar rats compared to government PMT biscuits. Our findings surpass those of interventions using Moringa leaf flour, where the trend of weight gain in the intervention group was lower than the normal rat group[16]. Similarly, interventions using biscuits made from pumpkin seeds have been shown to increase the body weight of malnourished Wistar rats[17]. Some research on toddlers also yielded similar results. Providing Mama Rani biscuits to undernourished toddlers contributed to an increase in their body weight[18]. We attribute the higher weight gain in the group of malnourished Wistar rats fed Tumiz biscuits to the complete nutritional content of the product, especially its energy, protein, and fat content.

Nutrients like carbohydrates and fats provide energy and building blocks for the body, while protein plays a crucial role in tissue formation. Consumption of foods rich in fat, carbohydrates, and protein can lead to an increase in body weight[19]. The administration of Tumiz biscuits also increased the albumin levels of malnourished Wistar rats. We observed that the increase in albumin levels in the intervention group was higher than in the two control groups that did not receive the biscuit supplementation intervention, namely groups K1 and K2. Both control groups experienced decreased albumin levels. However, compared to the Ministry of Health biscuit intervention group, the increase in albumin levels in the Tumiz biscuit intervention group was still lower than the results of the government program biscuit intervention. Our findings align with several previous studies, both in animal and human subjects. Rahmawaty (2009) reported that the intervention of tempebrutul biscuits fortified with iron (Fe) and zinc (Zn) could increase body weight and albumin levels in experimental rats suffering from malnutrition[20]. However, providing moringa cookies increased protein intake and body weight but did not been able to increase albumin in undernourished children[21]. Additionally, while the infertvention of tempe bengkuang formula improved nutritional status, it did not increase albumin levels in undernourished toddlers. Conversely, a significant increase in albumin levels occurred in the intervention group of the Kemenkes biscuit program. Providing additional food in the form of multigrain nutritious biscuits was shown to increase

body weight and reduce the prevalence of wasting in malnourished children[22].

Growth

We observed consistent growth in body length of Wistar rats across all groups. Group K4 exhibited a higher growth rate compared to the normal rats in group K1. Likewise, group K2, which received the biscuit intervention program, showed growth patterns resembling those of normal rats, albeit slightly lower than group K4. On the other hand, group K3 which received normal food intervention, experienced slower growth towards the end of the intervention, though this did not significantly affect the increase in body length.

The change in body length of malnourished Wistar rats in group K4 and group K2 during the 8-week intervention was 5.5 cm and 4.25 cm, respectively. This increase in body length for the two groups was greater than that observed in the normal rat group (K1) and control group K3, which measured 3.93 cm and 3.68 cm, respectively. We also noted the elevation of IGF-1 levels in groups K4 (2.052 µmol/L) and K2 (2.360 µmol/L). Different result were shown in the group K1 (-2.021 µmol/L) and K3 (-0.121 µmol/L) where experienced a decrease in IGF-1 levels. These findings suggest that the feeding intervention in the form of functional multigrain biscuits (Tumiz) can enhance the body length growth of malnourished rats. Although the difference in body length increase was not statiscally significant, the body length growth rate of the Tumiz biscuit intervention group was higher than that of the normal rat group. Malnutrition leads to decreased growth, as reflected by lower IGF-1 levels. Malnourished rats typically exhibited lower IGF-1 levels compared to normal rats, as observed at the beginning (pretest) of our study. Our finding is supported by the finding of a study in Burkina Faso that shows low IGF-1 levels in malnourished children. This study suggested that differences in food intake may contribute to variations in IGF-1 levels. IGF-1 concentration is positively correlated with the growth and nutritional status of children[23].

The Tumiz biscuit intervention can gradually increase IGF-1 levels and body length in rats. The effect of our intervention mirrored that of the Ministry of Health's program biscuits, resulting in a growth rate of rats at the end of the study higher than that of normal rats. We attribute this effect to the comprehensive nutritional content of Tumiz biscuits, including protein, fat, vitamin A, calcium, and zinc. These nutrients play crucial role in linear growth. Tumiz, made from local functional foods such as soybean, green bean, and sago worm, contains essential amino acids and fatty acids vital for growth[24,13]. The content of these nutrients in the Tumiz biscuits resemble the nutrients in the Ministry of Health program biscuits, which have been shown to increase children's body length in the previous study[25]. This finding corroborates previous research indicating that processed ingredients and products, such as fish, can mitigate impaired height growth in stunted children[26]. Tumiz biscuits also possess high micronutrient potential, particularly zinc, calcium, phosphorus, and iron, essential for supporting children's height growth[27].

Rats supplemented with Tumiz biscuits exhibited increased linear growth, as reflected by changes in height during the intervention. These results aligned with previous findings in toddlers through the intervention of local snacks enriched with shellfish flour[26]. The high micronutrient levels in Tumiz biscuit supplements are believed to support this growth. Micronutrients, especially zinc, play a crucial role in growth. Zinc-enriched diets have been shown to enhance linear growth and reduce the prevalence of growth disorders in children under five years old[17]. Another important nutrient contained in the Tumiz biscuits is β-carotene, which is beneficial for supporting infant growth. Although we did not measure retinol levels in this study, there is a positive correlation between serum retinol and IGF-1 levels[28]. Several previous studies have highlighted the role of vitamin A in growth indicators. Studies in healthy infants in Indonesia[29] and newborns in Canada[30], showed lower IGF-1 levels in vitamin A-deficient toddlers compared to normal children.

CONCLUSION AND RECOMMENDATIONS

Administration of Tumiz biscuits showed notable effects in increasing the body weight of malnourished Wistar rats; however, this did not lead to an increase in albumin levels. In contrast, intervention with Tumiz biscuits showed promising results in increasing body length and IGF levels in malnourished Wistar rats. Further research is needed in the form of clinical trials to determine the effectiveness of Tumiz biscuits in improving the nutritional status and growth of undernourished children.

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